

that a woman near the menopause many times became pregnant without apparently giving any indication of pregnancy, believing that the cessation of menses was due to the menopause. Without positive signs, which are evident only from the fourth to the fifth month, a physician hesitated to make a diagnosis.

The advent of the Aschheim-Zondek test was one of the greatest contributions to the obstetrical art since prenatal care. It proved, in a small series of cases, that an early diagnosis of pregnancy could be made in not less than one hundred hours. Sterile technique, a microscopical examination, and the raising and care of a large number of mice or rats were the only requisites for accurate diagnosis of early pregnancy.

Ebersson and Silverberg later reduced the time for the interpretation of the test to forty-eight hours by separating the ovarian hormones and concentrating the pituitary hormones.

These methods are, however, impractical as they require laboratory technique and a microscopical examination.

Friedman, in 1929, developed the rabbit test and with a small series proved that his method was equally as accurate as the Aschheim-Zondek method.

Doctor Dorn and his associates, with a much larger series, have proved conclusively that the Friedman test is accurate and simple to perform. No sterile technique is necessary and the test can be made in any office.

The great advantage of the rabbit test will be the early diagnosis of pregnancy in those patients whose welfare is at stake and in whom the continuation of pregnancy would be inadvisable. With further study, there is no doubt that the rabbit test will be the standard test for pregnancy in the future.



R. GLENN CRAIG, M. D. (490 Post Street, San Francisco).—Since the first announcement of Aschheim and Zondek, reporting a high percentage of accuracy in the test for pregnancy which bears their name, numerous reports have appeared in the literature confirming their statistics. These have usually shown the test to be 95 per cent, or more, accurate, although Mazer and Hoffman report only 75 per cent accuracy. Attempts at modification of the original technique of Aschheim-Zondek have not given as good a result.

One objection to this test has been the four or five-day interval which must elapse before the results are known. Recently Ebersson and Silverberg have proposed a quicker method, requiring thirty-six to forty-eight hours with equally good results.

Another objection to the use of immature mice or rats is the large breeding stock which must be kept on hand to insure a sufficient supply of immature animals. Since the rabbit has no regular recurring sexual cycle, as true ovulation only occurs after coitus (one of the few examples of economy in nature), the use of this animal would obviate this objection if the results were equally satisfactory. The results reported here speak for the accuracy, and are in agreement with other figures available when the rabbit has been used as the experimental animal. "Time will tell" which is most desirable.

Of course we must not forget that, to be of value, the report should include, or preferably be limited to, patients in whom the diagnosis of pregnancy is not easily made by digital examination. This would include both the early pregnancies, which should be less than two weeks after a missed menstrual period, and the abnormal pregnancies, such as an extra-uterine pregnancy, a pregnancy associated with myomati uteri, or the death of the fetus. Any effort to extend the accuracy of medical diagnosis, such as this, is to be commended.

CINCHOPHEN POISONING*

REPORT OF CASE

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THE sad results of clinical disaster have furnished convincing evidence of the toxicity of many compounds which had been hailed as safe and harmless after the most exacting laboratory investigation. Cinchophen, a phenyl quinolin carboxylic acid, was produced in the course of researches in synthetic organic chemistry less than a half century ago.¹ Chemically related to the quinolin derivatives, it possesses pharmacological similarities to the salicylates.² Its clinical value was suggested by the studies of its effect on uric acid excretion in 1908.³ Since then its use has increased rapidly all over the world. It was early accepted by the Council on Pharmacy of the American Medical Association and incorporated in the Pharmacopeia of the United States.⁴

Elaborate pharmacological investigations by many workers, both in this country and abroad, consistently showed an absence of harmful effects from doses far exceeding any therapeutic expectations.⁵ Most of the textbooks in use throughout the United States still assert that these preparations are practically devoid of danger.⁶ Only in the last edition of New and Nonofficial Remedies is any mention made of possible fatalities from its use.⁷ Clinical testimonials to its safety were also abundant.⁸ Minor skin reactions were occasionally reported, but they were usually considered inconsequential rarities.⁹

Only during the past five years, it seems, have any deaths from this cause been recognized, but the continuously increasing reports of these fatalities leave little doubt as to their real existence and importance.¹⁰ The actual number of persons who have used cinchophen derivatives is undoubtedly large, but when it is remembered that the usual indications for its use are often painful, but rarely fatal conditions in themselves, the incidence of fatal poisoning may not be disregarded. The following case report illustrates this fact.

REPORT OF CASE

A white woman, age nineteen, was admitted to the Olive View Sanatorium of Los Angeles County on December 17, 1930, and diagnosed as having "incipient tuberculosis." Her father and one sister had died of tuberculosis. She had always been a delicate child, had been severely burned at the age of one year, and again extensively burned over the entire right side and back when fifteen years of age. She had had measles, whooping-cough, chorea, chicken-pox and mumps, and her tonsils had been operated on twice under ether anesthesia. She had had typhoid fever at the age of six, and again four years later. Her appendix had been removed one year ago. She complained of anorexia, constipation, lassitude and undue fatigue, slight loss of weight, occasional pain in the chest, swelling of the left ankle, and slight elevation of temperature.

Physical examination revealed no signs of pulmonary pathology. There was a fluctuant swelling posterior to the left external malleolus, painful on walk-

* Editor's Note.—For brief statement concerning "Toxicity of Cinchophen and Safety of Neocinchophen," see Journal A. M. A., August 8, 1931, page 409. Also page 307, in this issue of California and Western Medicine.

ing, but not reddened or tender. There was a vaginal discharge and venereal warts at the vulva, but smear showed no Gram-negative diplococci. Wassermann test was negative. The white blood count was 7200; hemoglobin, 75 per cent; urine negative for albumin or pus; and sputum absent except on one occasion, when it was negative for acid-fast bacilli. The vital capacity was 2700 cubic centimeters. Sedimentation rate was only moderately accelerated, and temperature was normal during nearly all of her sanatorium stay. The x-ray showed nothing characteristic for pulmonary tuberculosis.

In addition to general measures, tonics, sedatives and laxatives, and local treatment to the vulvar condylomata and to the ankle, cinchophen, grains seven and one-half, three times a day, was started February 28, 1931, and continued until April 7, a total of about fifty-five grams. During this time the pain and swelling in the ankle abated. On April 6, however, the patient complained of pain on urinating, and nausea, and on the following day began to vomit. A dull intermittent pain was felt in the right iliac region, worse after eating, and partly relieved by hot applications. The urine had been dark red in color for a month, the stools were hard and occasionally appeared clay-colored. A yellowish discoloration was noted first in the eyes, later increased, and on April 12 jaundice of the skin was reported. The jaundice, nausea, and abdominal pain persisted and increased. The urine tests were positive for bile pigments and bile salts, and the Van den Bergh test in the blood serum was positive direct, with a reading of fifteen milligrams.

Cinchophen poisoning was suspected, and active measures taken to treat it, including intravenous injections of glucose and insulin. On April 19 the patient developed severe right-sided abdominal pain with nausea and vomiting, and a white blood count of 20,000 which later rose to 39,000. An exploratory laparotomy, performed under spinal anesthesia, revealed a distended stomach, but otherwise a normal abdomen. The patient became progressively weaker, labial herpes, hiccough, choreiform movements and delirium appeared, and death followed on April 24.

Necropsy.—At necropsy a small calcified old tuberculous focus was found in the right lung, with no evidence of activity. In the lower parts of both lungs were areas of early patchy consolidation, apparently hypostatic. The stomach was greatly distended. The liver was small, weighing 1200 grams, homogeneous in appearance, with normal liver markings indistinct. Sections showed areas of necrosis most marked in the neighborhood of the central veins, with relative increase in the connective tissue stroma of the liver. The gall-bladder was small and showed no evidence of obstruction or infection. The spleen weighed 1400 grams and the Malpighian corpuscles were somewhat prominent. The small intestine, particularly in the lower ileum, contained many enlarged congested lymphoid follicles. The kidneys showed slight cloudy swelling. The ovaries contained multiple bloody cysts.

PATHOLOGY

The pathological picture produced by cinchophen poisoning is quite definite and consistent. In practically every instance the liver is the main organ involved. A toxic necrosis of the liver cells, followed occasionally by evidence of cirrhosis or fibrotic changes, with little or no sign of inflammatory reaction, is the usual finding. Symptoms of biliary obstruction similar to those of acute catarrhal jaundice develop, only occasionally accompanied by those of portal obstruction with ascites and edema.

The pathogenesis of cinchophen poisoning is not so readily ascertained. That an overdose of cinchophen might produce liver damage appears plausible in view of the high choleric effect of therapeutic doses,¹¹ the impaired liver function

tests reported following a week after the initial injection of the drug,¹² and the more recent work on liver damage in animals produced by overdosage of the drug.¹³ On the other hand, the fact that some patients succumb to such trivial amounts while others appear to tolerate enormous doses suggests the importance of some individual idiosyncrasy or predisposition.

COMMENT-ON LITERATURE

The eighty instances of cinchophen poisoning so far reported¹⁴ show a marked preponderance of the female sex and the older years of life. Previous liver damage, as from typhoid fever, hepatitis or cholecystitis and other conditions, have been frequently noted. The amounts taken, and the period of administration vary widely, and bear no constant relationship to the fatal outcome, but the intravenous administration seems to be unduly unfortunate. The positive skin tests reported in some susceptible individuals, and the occurrence of symptoms on use after a period of absence from the drug in others suggests an allergic interpretation, but the clinical and pathological findings are opposed to this explanation.

Cinchophen and its derivatives are marketed under more than two dozen different names. Poisonings have been already reported from cinchophen, atophan, phenylcinchoninic acid, diiodoatophan, biloptin, atophanyl, oxyl iodid, atquinol, atochinol, leucotropin, monoiodocinchophen and from "Weldona," "Van Ards," "Cass," and "Harrell's" rheumatism cures. No instances have been shown to be due, as yet, to the use of neocinchophen or "tolysin," the methyl ethyl ester of cinchophen. Whether it is an exception, and harmless, is uncertain.

Despite the efficacy of cinchophen and its derivatives in controlling pain in a large number of cases, its toxicity renders it far too dangerous to use in clinical conditions that are otherwise associated with almost no fatalities. Neither small dose, intermittent administration, nor early discontinuance provides any security. The use of these drugs is fraught with definite danger of fatal consequences in a proportion too high to be ignored. The physician is not justified in subjecting the patient to so great a risk. "Primum nil nocere."

Olive View Sanatorium.

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* Additional references, which are not keyed to the above text, will be given in the reprints.